The Relationship of Blood Lead to Systolic Blood Pressure in a Longitudinal Study of Policemen

by Scott T. Weiss,*† Alvaro Munoz,‡ Amy Stein,† David Sparrow,§ and Frank E. Speizer†

We examined the relationship of blood lead level to systolic and diastolic blood pressure in a longitudinal study of 89 Boston, MA, policemen. At the second examination blood lead level and blood pressure were measured in triplicate. Blood pressure measurements were taken in a similar fashion in years 3, 4, and 5. Multivariate analysis using a first-order autoregressive model revealed that after adjusting for previous systolic blood pressure, body mass index, age, and cigarette smoking, an elevated blood lead level was a significant predictor of subsequent systolic blood pressure. Bootstrap simulations of these models provided supporting evidence for the observed association. These data suggest that blood lead level can influence systolic blood pressure even within the normal range.

Introduction

A variety of epidemiologic studies have suggested a small but statistically significant effect of blood lead level on systolic blood pressure and suggest a weaker association with diastolic blood pressure as well (1-4). These studies were cross-sectional in design and involved large numbers of subjects.

We examined the relationship between blood lead level and longitudinal change in blood pressure in a small group of policemen under observation for health outcomes related to environmental work exposures. Using computer-intensive statistical techniques, we demonstrated an effect of blood lead on systolic blood pressure similar to that seen in large cross-sectional surveys.

Materials and Methods

The populations of subjects studied has been characterized in previous reports (5-7). The men of two separate units of the Boston Police Department were seen at their respective station houses during normal working hours. Preliminary observations included measures of height, made with subjects in stocking feet, and weight of subjects wearing street clothing, without jackets and usual accessory equipment. A detailed questionnaire containing demographic, smoking, occupational, and residential history, and a modified version of the British Medical Research Council Respiratory Disease Questionnaire were administered by trained interviewers. In addition, information about cardiac complaints were obtained by a standard version of the Rose Angina Questionnaire (8).

Pulmonary function testing was measured on a water-filled spirometer and is the subject of a separate report (7). A blood specimen was obtained to determine hematocrit concentration and to make peripheral smears to assess basophilic stippling. Blood lead concentration was determined on a small sample of subjects to validate their traffic exposure histories. Blood lead concentration was determined using the technique of atomic absorption spectrophotometry (9). Blood pressure was measured with a random zero blood pressure machine to minimize digit preference. With the subject seated, systolic pressure and fifth-phase diastolic pressure was measured in the left arm to the nearest 2 mm Hg.

The study was a longitudinal investigation with initial screening beginning in 1969-1970 and with

*Charles A. Dana Research Institute and the Harvard Thorndike Laboratory of the Beth Israel Hospital and Department of Medicine, Harvard Medical School, Boston, MA 02115.

†Channing Laboratory, Brigham and Women's Hospital and Department of Medicine, Harvard Medical School, Boston, MA 02215.

‡Department of Epidemiology, Johns Hopkins School of Public Health, Baltimore, MD 21218.

§Normative Aging Study, VA Outpatient Clinic, Boston, MA.

observations completed in 1974–1975. Blood pressure (in mm Hg) was recorded in years 2 through 5. The mean of triplicate measures of systolic pressure and diastolic pressure at each visit was used for analysis. Age in years, body mass index (in kg/m²), and current smoking status (recorded as 1 = current, 0 = never or exsmoker) were available for years 1 through 5. Current cigarette smokers were defined as subjects who smoked as many as one cigarette a day in the study year. Blood lead values (in µg/100 mL) were collected only in year 2. Based on the distribution of blood lead values in our sample and in that of the United States population (10), blood lead values were divided into high (≥ 30 µg/100 mL) and low (≥ 20 and ≤ 30 µg/100 mL) groups for purposes of the regression analysis. This gave comparable numbers of subjects in each category. These two groups were compared with our reference group in which values were ≤ 20 µg/100 mL.

To examine the relationship of blood lead concentration to change in blood pressure over the 4 years of the study, a Markov type autoregressive model was used (11). In this model, blood pressure (systolic or diastolic) at time $t(Y_t)$ is related to blood pressure at t-1 (Y_{t-1}) and the levels of other covariates at time t or at previous time points. Specifically, the model takes the form

$$Y_t = A + C(Y_{t-1}) + B_1 X_{1t} + B_2 X_{2t} + ... + e_t$$

This model has several advantages for the analysis of longitudinal data sets. Specifically, the model uses the data efficiently since any individual for whom complete data are available for any two consecutive years (t and t-1) will contribute data to the model. Secondly, the model does not impose a particular shape (i.e., linearity) on the relationship between the dependent and independent variables. Finally, this model can be fitted using ordinary statistical software packages. The model assumes that the residual e's are independent with constant variance (θ^2) both within and between individuals. An additional assumption is that the relationship between the outcome variable and the independent variables is the same for all individuals (fixed effects model).

A cross-validation was undertaken to determine if the magnitude and significance of the regression

coefficients obtained for the blood lead variables were the result of the disproportionately large contribution of values from a few individuals (12). To determine if an individual was an outlier, we used a modification of Tukey's fences applied to the cross-validation exercise (13). After the full cross-validation, we determined the subject whose exclusion has the largest influence on any regression coefficient (measured in units of interquartile range away from either the first or the third quartiles of the distribution of the values of all the regression coefficients obtained from the cross-validation). This individual was then removed and the cross-validation repeated. This process was continued until all regression coefficients resulting from a cross-validation exercise were within five interquartile range units away from either the first or the third quartiles.

To determine the variability of the regression coefficients, without the assumption that the residuals are normally distributed, a bootstrap analysis was performed (14). In this analysis, we generated 1000 (bootstrap) samples equal in size to the original sample by randomly sampling with replacement from the original pool of individuals. The distribution of the coefficients for the bootstrap samples can be considered as though they were coming from real samples, and thus they provide a measure of the statistical precision of the original estimates on the regression coefficients.

Results

Table 1 presents the cross-sectional data for the variables used in the longitudinal regression analysis. In the second year of the study, when blood lead was initially measured, the average subject was a normotensive, middle-aged man who was overweight. Roughly half of all subjects were cigarette smokers, and one-quarter of all subjects had a concentration of blood lead ≥ 30 µg/100 mL.

A total of 95 men had blood lead determinations out of a total of 314 (30%). Information for six men was missing for all covariates. The other 89 men were entirely comparable to men without blood lead measurements for all covariates (17).

We modeled the level of current systolic blood pres-

Table 1. Cross sectional data for blood pressure, age, body mass index, blood lead, and smoking for Boston policemen by study year.

Parameter	Year 2			Year 3			Year 4			Year 5		
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
Systolic pressure, mm Hg	246	126.7	20.1	199	126.6	17.6	149	128.7	17.6	194	130.9	17.3
Diastolic pressure, mm Hg	246	84.8	13.8	198	83.9	10.7	167	82.7	11.3	194	85.4	10.6
Age, years	267	46.6	8.5	200	47.3	9.0	192	48.1	8.5	193	49.3	8.1
Body mass index, kg/m²	253	27.8	3.2	200	28.1	3.3	189	28.1	2.9	185	28.0	3.2
Blood lead, µg/100 mL												
< 20	36	40.4										
20–29	33	37.1										
≥ 30	26	22.5										
Current smokers, %	182	46.1%		213	47.8%		206	49.9%		192	48.4%	

sure at time t as a function of previous systolic blood pressure at $t-1$, other independent variables known to influence blood pressure and blood lead (Table 2). Seventy individuals provided 162 pairs of data (consecutive examinations) for this regression. There was a statistically significant association ($p = 0.036$) between a high (≥ 30 µg/100 mL) level of blood lead and subsequent systolic blood pressure. Similar modeling was performed for diastolic blood pressure, but no significant association was found (15).

To investigate whether the observations noted above were the product of a few influential points, an iterative cross-validation analysis was undertaken. For systolic pressure, three individuals were excluded so that all regression coefficients resulting from a cross-validation were within five interquartile range units away from either the first or the third quartile. The regression was repeated without the data of these subjects, and the results are presented in Table 3. Although the association betwen high systolic pressure and high blood lead level noted above is only of borderline significance ($p = 0.097$), the magnitude and direction of the observed relationships are essentially unchanged. On the other hand, the effect of the other covariates (age, body mass index, and smoking) is more consistent with known effects of these variables on blood pressure. In summary, the exclusion of influential points improved the relationship between systolic pressure and the independent variables (prior systolic

pressure, body mass index, age, smoking status) and did not dramatically change the relationship between systolic pressure and high blood lead. This provides further support for the observed association of these variables.

In an attempt to estimate the variability (without the normality assumption) of the parameter estimates for blood lead, bootstrap simulations of the model were performed for systolic pressure (Fig. 1). For this purpose, we generated 1000 separate random samples by sampling with replacement from the 70 subjects who provided data on systolic pressure. Figure 1 suggests that the coefficient for high blood lead is greater than zero with a mean value of 5.8 (C. I. 90%, 1.5–11.5 mm Hg). This bootstrapping simulation confirms the association between high blood lead and high systolic pressure without the need to assume normality of the residuals.

Discussion

This longitudinal analysis demonstrates that blood lead levels at the upper range of normal are associated with mild elevations in systolic blood pressure in normotensive working men. The powerful statistical techniques used in this analysis have allowed us to estimate an effect of blood lead on blood pressure quite similar to that observed in large cross-sectional surveys (2–4). It is worth noting that our modeling approach would have allowed for repeated measurements of blood lead. Greater precision in the measure of exposure should have enhanced the statistical power of the analysis.

Selection bias is unlikely to account for the observed

Table 2. Relationship of systolic blood pressure in Boston policemen at time t to prior systolic blood pressure, body mass index, age, smoking, and blood lead.[a]

Variable	Coefficient	SE	p
Intercept	125.383		
Prior blood pressure, 127 mm Hg	0.518	0.059	< 0.001
Body mass index, 28 kg/m²	0.580	0.343	0.093
Age, 47 years	0.176	0.132	0.185
Smoker[b]	2.324	2.082	0.266
Blood lead, low[c]	0.224	2.251	0.921
Blood lead, high[d]	5.804	2.748	0.036

[a]Regression was done on 162 pairs contributed by 70 subjects.
[b]1 = yes; 0 = no.
[c]Low = 20–29 µg/100 mL.
[d]High = ≥ 30 µg/100 mL.

Table 3. Relationship of systolic blood pressure in Boston policemen at time t to independent variables excluding influential points.[a]

Variable	Coefficient	SE	p
Intercept	125.357		
Prior blood pressure, 127 mm Hg	0.497	0.064	< 0.001
Body mass index, 28 kg/m²	0.655	0.330	0.049
Age, 47 years	0.210	0.130	0.108
Smoker[b]	4.446	2.066	0.033
Blood lead, low[c]	−1.415	2.233	0.527
Blood lead, high[d]	4.467	2.672	0.097

[a]Regression was done on 155 pairs contributed by 67 subjects.
[b]1 = yes; 0 = no.
[c]Low = 20–29 µg/100 mL.
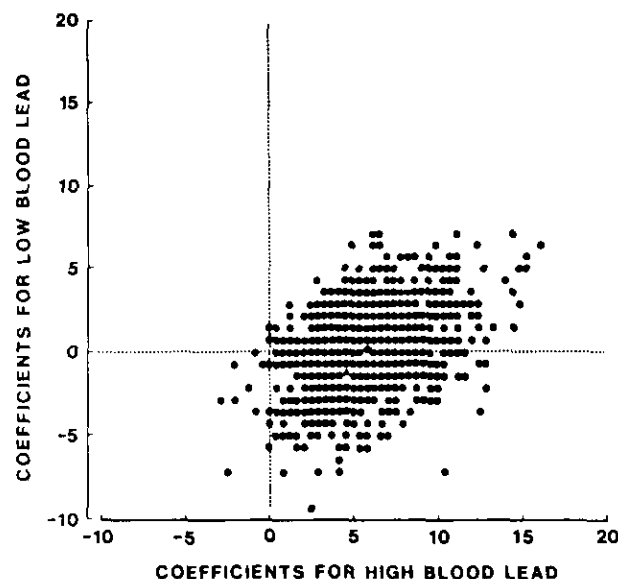[d]High = ≥ 30 µg/100 mL.

FIGURE 1. Plot of 1000 bootstrap coefficients for high and low blood lead effect on systolic blood pressure. One dot may represent multiple data points. (*)Coefficient for blood lead including all subjects, Table 2; ($\triangle$) coefficient for blood lead excluding influential subjects, Table 3.

relationships, as subjects with blood lead were essentially similar subjects without blood lead (17). In addition, no appreciable selective loss to follow-up could be observed in this cohort (Table 1).

In addition to possible bias, the small number of subjects could influence the precision of the regression coefficients. The cross-validation and subsequent study of influential data points (Table 3) provide an estimate of the smoking effect more consistent with published data than that observed with all the data (Table 2). In addition, the dose-response relationship for low and high blood lead is more internally consistent when the influential data points are excluded (Table 3).

The influential points were excluded in a blinded fashion, i.e., without regard to the magnitude or directionality of their effect on the parameter estimates. Although the exclusions do influence statistical significance, the parameter estimates for the effect of high blood lead on systolic pressure are similar in both analyses (Tables 2 and 3). This suggests that our results are not driven by data from a few individuals, an important consideration more likely in a small data set.

The bootstrap analysis assesses the statistical precision for the effect of blood lead on blood pressure and indicates that the 90% confidence interval for the parameter estimate for the effect of high blood lead (i.e., ≥ 30 µg/100 mL) on systolic pressure ranges 1.5 to 11 mm Hg. What remains unclear is the reason for the elevation in blood lead in these men.

These 90% confidence limits encompass all of the point estimates from larger cross-sectional surveys. Indeed, the estimate of a 5 mm Hg increase in systolic blood pressure with high blood lead is almost identical to that observed in NHANES with 8000 subjects (3,4).

Previous investigations by Pocock et al. (15) and Shaper et al. (16) have suggested a role for both alcohol consumption and cigarette smoking as environmental sources of lead exposure other than drinking water. We tested alcohol in our model and could find no independent effect of alcohol consumption on blood pressure either cross-sectionally or longitudinally. The fact that blood lead contributed independently to our model (Tables 2 and 3) when cigarette smoking was included suggests that blood lead level itself, rather than cigarette smoking-induced blood lead elevation, has an influence on systolic pressure.

Recently, calcium intake has been shown to influence blood pressure and blood lead (18). We have no information on calcium for this cohort and thus could not examine this relationship.

Clearly, further epidemiologic and physiologic work is necessary to elucidate the mechanisms for the blood lead-blood pressure relationship. However, there seems to be remarkable consistency in the epidemiologic data, suggesting a small but consistent increase in systolic blood pressure with elevated blood lead levels.

REFERENCES

1. Jhaveri, R. C., Lavorgna, C., Dube, S. K., Glass, L., Khan, F., and Evans, H. E. Relationship of blood pressure to blood lead concentrations in small children. Pediatrics 63: 674–676 (1979).
2. Pocock, S. J., Sharper, A. G., Ashby, D., Delves, T., and Whitehead, T. P. Blood lead concentration, blood pressure and renal function. Br. Med. J. 289: 872–874 (1984).
3. Pirkle, J. L., Schwartz, J., Landis, J. R., and Harlan, W. R. The relationship between blood lead levels and blood pressure and its cardiovascular risk implications. Am. J. Epidemiol. 121: 246–258 (1985).
4. Harlan, W. R., Landis, J. R., Shmouder, R. L., Goldstein, N. G., and Harlan, L. C. Blood lead and blood pressure: Relationship in the adolescent and adult U.S. population. JAMA 253: 530–534 (1985).
5. Speizer, F. E., and Ferris, B. G., Jr. Exposure to automobile exhaust. I: Prevalence of respiratory symptoms and disease. Arch. Environ. Health 26: 313–318 (1973).
6. Speizer, E. E., and Ferris, B. G., Jr. Exposure to automobile exhaust. II: Pulmonary function measurements. Arch. Environ. Health 26: 319–324 (1973).
7. Burgess, W., DiBeradinis, L., and Speizer, F. E. Exposure to automobile exhaust. III: An environmental assessment. Arch. Environ. Health 26: 325–329 (1973).
8. Rose, G. A., and Blackburn, H. Cardiovascular survey methods. WHO Monograph Series No. 56, 5–188 (1968).
9. Delves, H. T. A micro–sampling method for the rapid determination of lead in blood by atomic–absorption spectrophotometry. Analyst 95: 431–438 (1970)
10. Mahaffey, K. R., Annest, J. J., Robert, J., and Murphy, R. S. National estimates of blood lead levels: United States, 1976–1980. N. Engl. J. Med. 307: 573–579 (1982).
11. Rosner, B., Munoz, A., Tager, I. B., Speizer, F. E., and Weiss, S. P. The use of an autoregressive model for the analysis of longitudinal data in epidemiological studies in medicine. Stat. Med. 4: 457–468 (1985).
12. Mosteller, E., and Tukey, J. W. Data Analysis and Regression. Addison Wesley, Reading, MA, 1977.
13. Tukey, J. W. Exploratory Data Analysis. Addison Wesley, Reading, MA, 1977, pp. 43–45.
14. Efron, B. The Jackknife, the Bootstrap and Other Resampling Plans. Society for Industrial and Applied Mathematics, Philadelphia, 1982.
15. Pocock, S. J., Shaper, A. G., Walker, M., Wale, C. J., Clayton, B., Delves, T., Lacey, R. F., Packham, R. F., and Powell, P. Effect of tap water lead, water hardness, alcohol, and cigarettes on blood lead concentrations. J. Epidemiol. Commun. Health 37: 1–7 (1983).
16. Shaper, A. G., Pocock, S. J., Walker, M., Wale, C. J., Clayton, B., Delves, H. T., and Hinks, L. Effects of alcohol and smoking on blood lead in middle–aged British men. Br. Med. J. 284: 299–302 (1982).
17. Weiss, S. T., Munoz, A., Stein, A., Sparrow, D., and Speizer, F. E. The relationship of blood lead to blood pressure in a longitudinal study of working men. Am. J. Epidemiol. 123: 800–808 (1986).
18. McCarron, D., Morris, C. D., Henry, H. J., and Stanton, J. L. Blood pressure and nutrient intake in the United States. Science 224: 1392–1394 (1984).